TOBACCO INDUSTRY RESEARCH COMMITTEE #183A
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.
(cr. #153)

Application For Research Grant

Date: November 24, 1958

1. Name of Investigator: Roe E. Wells, Jr., M.D.

2. Title: Associate in Medicine, Peter Bent Brigham Hospital; Clinical Associate in Medicine, Harvard Medical School

3. Institution & Address: Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts

4. Project or Subject: Studies of the Antinicotinic action of the benzyl analog of serotonin and similar antiserotonin drugs.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

Studies will be carried out on patients with chronic pulmonary disease, patients with arteriosclerotic heart disease and normal subjects. Recordings of pulse, blood pressure, minute ventilation, pulmonary compliance and flow resistance (intra-esophageal balloon technique) and in certain cases electroencephalograms will be carried out as follows: Normal subjects and patients will be studied at rest; after initial baseline observations either intravenous nicotine (1 to 3 mgs. intravenously) will be administered or patient given two cigarettes to smoke in measured period of time followed by repeat studies within 2 minutes end of mg nicotine or cigarette. The benzyl analog of serotonin (1-Benzyl-2-methyl-5-methoxy tryptamine hydrochloride) (BAS) will be given intramuscularly or by mouth (0.25 to 0.5 mgs./kg) and studies repeated at 30 minute and 60 minute intervals. The entire study will also be carried out again using BAS prior to nicotine or cigarette smoking to ascertain any blocking effect. (see #10 Additional information)

Chronic heavy smokers (60 cigarettes a day and over) as well as non smokers will also be studied during a 24-hour period in order to collect 24 hour urine samples for 5-hydroxy indole acetic acid (5HIAA) excretion before and after use of BAS. Studies will be repeated in the non smokers who are able to smoke as many cigarettes as feasible for 72 hours building up to 30 cigarettes or more a day and repeating the use of BAS and the study. Similarly if feasible, the reverse study of 5HIAA excretion in the chronic smoker before and after cessation of smoking (the after representing no smoking in any form for at least 2 weeks). Pending completion of studies upon BAS it is intended to repeat similar observations with the use of mmk chlorpromazine and other phenothiazine derivatives.

6. Budget Plan:

Salaries	$1,230
Expendable Supplies	2,275
Permanent Equipment	765
Overhead 15%	640
Other	--
Total	4,910

7. Anticipated Duration of Work: One year January 1, 1959 to December 31, 1959

8. Facilities and Staff Available: General facilities of a 236 bed medical-surgical hospital with pulmonary function laboratory capable of carrying out analysis of pulmonary function involving lung volumes, mechanics of respiration, bronchospirometry, alveolar ventilation, blood gas analysis, pH determinations, fluoroscopy of the heart and chest and immediately adjacent electroencephalographic equipment.

5 physicians
3 full-time (1 laboratory director 2 research fellows)
2 part-time (1 cardiologist 1 chest physician)
1 senior technician (10 years experience as cardiopulmonary technician)

9. Additional Requirements: None

10. Additional Information (Including relation of work to other projects and other sources of supply): (includes preliminary studies and work now in progress) Tobacco has been said to "tranquilize the spirit" (1). Theoretical considerations regarding this well recognized action of smoking tobacco in producing a certain amount of tranquilization or relief of tension and anxiety led us to the hypothesis that this action may be similar to the tranquilization produced by certain drugs like reserpine. It is currently generally accepted that this reserpine effect is associated with the release of serotonin in certain areas of the brain (2, 3). It has therefore been postulated by us that nicotine may likewise act on the central nervous system by the liberation of serotonin. It has been well established that nicotine has an important effect upon the autonomic ganglion cells. These effects in general consist first in stimulation and later in depression of these cells. There is some evidence that serotonin is involved in the transmission of the nerve impulse at this level (4). However, to our knowledge, no studies involving the use of nicotine in humans or of serotonin antagonists to study this action have been reported. If our hypothesis regarding the action of nicotine on the nervous system is correct, we should be able to block some of the important pharmacological effects of this agent by the use of antiserotonin substances. (Continued on page 2a).

Signature
Director of Project Wells, Jr.

/s/ F. Lloyd Mussells
Business Officer of the Institution

We have chosen to begin our investigation of this possible action by utilizing BAS (benzyl analog of serotonin), a chemical compound synthetized by Woolley (5) for the specific purpose of blocking serotonin action.

Preliminary Observations: Nicotine has been administered intravenously to a series of normal human subjects, including smokers and non-smokers. Measurement of respiratory rate, minute volume, pulmonary airflow resistance, and compliance, blood pressure, electrocardiograms and in selected cases electroencephalograms have been recorded. The subjects have also been observed clinically for evidence of pallor, sweating, or syncope. Their subjective reactions have also been recorded. BAS has been administered intramuscularly to these subjects after these observations and before and after the intravenous administration of nicotine. It has been consistently noted in the cases studied thus far that this serotonin blocking agent also appears to block some of the important pharmacologic and physiologic effects of nicotine on the nervous and cardiovascular systems. Similar observations have been begun on previously studied patients with pulmonary emphysema and bronchial asthma who are known to have consistently predictable reactions from cigarette smoking, by administering BAS after cigarette smoking and noting the changes in the parameters described above when this antiserotonin agent is administered.

Further Studies: In relation to the above studies, an attempt is being made to determine whether the administration of nicotine intravenously results in an increase in the urinary excretion of 5-hydroxy indole acetic acid (5HIAA). Such an increase might be expected if nicotine causes the release of significant amounts of serotonin in the body. Along the same line of thought, the 24 hour excretion of 5HIAA is also being studied in groups of non smokers and smokers, including normal individuals and patients with broncho-pulmonary disease. (See cost of expendable supplies - cost of 5HIAA and other chemical analyses).

It is believed that these observations may yield information which will be of considerable interest from the point of view of a clearer understanding of the basic mode of action of nicotine in the body as a pharmacologic agent. It may also provide some avenues of approach for practical applications involving the use of niccotine blocking agents which might be found to counteract some of the undesirable pharmacologic effects of nicotine, while at the same time preserving the pleasure giving effect of tobacco smoking. In patients with certain types of cardiac or pulmonary disease who find it impossible to give up the smoking habit in spite of its effects upon them, some of the drugs which these studies may find effective might be important therapeutically.

The majority of equipment used in these studies has been purchased for studies of the mechanics of respiration by other research grants. The laboratory program which is involved in the study of respiratory mechanics in general has been supported by the Howard Hughes Medical Institute and the Massachusetts Heart Association. The specific study now underway most closely related to that proposed in this request concerns the effect of cold air inhalation upon the function of the heart and respiratory system.

Bibliography

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4. Himwich, H.E.: Psychopharmacologic Drugs. Science. 127: 59, 1958.

5. Shaw, E.N., and Woolley, D.W.: Methylserotonins as Potent Antimetabolites of Serotonin Active both in vitro and in vivo. J. Pharmacol. Expt. Therapy, 116:164, 1955.

6. Costa, E.: The Effects of Hallucinogenic and Tranquilizing Drugs on the Serotonin Evoked Uterine Contractions. Psychiat. Research Rept. 4:11, 1956.